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Registration Decision RD2013-01

Fluroxypyr

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Registration Decision for Fluroxypyr

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of Starane F Technical Herbicide and Starane II Herbicide, containing the active ingredient fluroxypyr, for postemergent suppression or control of kochia in industrial and non-cropland areas including roadsides, rights of way and industrial vegetation management areas.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

These products were first proposed for registration in the consultation document[1] Proposed Registration Decision PRD2012-18, *Fluroxypyr*. This Registration Decision[2] describes this stage of the PMRA's regulatory process for fluroxypyr and summarizes the Agency's decision, the reasons for it and provides, in Appendix I, a summary of comments received during the consultation process as well as the PMRA's response to these comments. This decision is consistent with the proposed registration decision stated in PRD2012-18.

For more details on the information presented in this Registration Decision, please refer to the Proposed Registration Decision PRD2012-18, *Fluroxypyr* that contains a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act*.

4 "Value" as defined by subsection 2(1) of *Pest Control Products Act* "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Fluroxypyr?

Fluroxypyr is a systemic and selective post-emergent herbicide that offers control of hard-to-kill annual broadleaved weeds such as kochia (2-8 leaf), cleavers (1-4 whorl), and chickweed (up to 8 cm) in small grain cereals and control of kochia in rangeland, permanent pasture, industrial and other non-cropland areas. Fluroxypyr is formulated as fluroxypyr-methylheptyl ester which, after predominantly foliar uptake, hydrolyses to fluroxypyr acid, which is the herbicidally active form of fluroxypyr. Fluroxypyr induces auxin-type responses and disrupts plant cell growth in the newly forming stems and leaves of susceptible plants.

Health Considerations

Can Approved Uses of Fluoroxypyr Affect Human Health?

Fluroxypyr is unlikely to affect your health when used according to label directions.

Potential exposure to fluroxypyr may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration. Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, technical grade fluroxypyr (acid or methylheptyl ester) was of low acute toxicity by the oral and dermal routes and was of slight toxicity by the inhalation route of exposure. Fluroxypyr was mildly irritating to the eyes and non-irritating to the skin, and did not elicit an allergic skin reaction. Consequently, the hazard signal words "CAUTION – POISON – EYE IRRITANT" are required on the label.

The acute toxicity of the end-use product Starane II Herbicide was low via the oral, dermal and inhalation routes of exposure. It was moderately irritating to the eyes and mildly irritating to the skin. It caused an allergic skin reaction in mice. Consequently, the hazard signal words "WARNING – EYE AND SKIN IRRITANT - POTENTIAL SKIN SENSITIZER" are required on the label.

In animals given daily oral doses of fluroxypyr over long periods of time, decreases in body weight gain and changes to the kidneys and adrenals were observed. Fluroxypyr did not damage genetic material and did not cause tumours in rats or mice. There was no indication that fluroxypyr caused damage to the nervous system or immune system. Fluroxypyr did not cause birth defects in the developing young, or effects on the reproductive system. When fluroxypyr ester was given to pregnant animals, a foetal variation (retrocaval ureter) was noted in the absence of maternal toxicity, indicating that the young were more sensitive to fluroxypyr than the adult animals. The risk assessment protects against the effects of fluroxypyr by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Occupational Risks From Handling Starane II Herbicide

Occupational risks are not of concern when Starane II Herbicide is used according to the proposed label directions, which include protective measures.

Workers who mix, load or apply Starane II Herbicide, as well as field workers re-entering freshly treated non-crop areas, can come in direct contact with fluroxypyr residues on the skin. Mixers, loaders and applicators may also be exposed by breathing sprays and mists. Therefore, the label specifies that anyone mixing/loading and applying Starane II Herbicide must wear coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves. The label also requires that workers do not enter treated industrial and non-cropland areas until residues have dried. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Fluroxypyr Is Introduced Into the Environment?

Fluroxypyr in the form of fluroxypyr-methylheptyl ester is non-persistent in the environment and transforms readily to fluroxypyr acid. Fluroxypyr-methylheptyl ester is expected to impact terrestrial plants and aquatic organisms, therefore, spray buffer zones are required during application.

Fluroxypyr-methylheptyl ester will enter the environment through application to industrial and non-cropland areas. Fluroxypyr-methylheptyl ester is non-persistent in the environment and has low potential to leach. Fluroxypyr-methylheptyl ester biotransforms in soil and aquatic systems

with hydrolysis as the predominant degradation mechanism. Fluroxypyr acid is slightly to moderately persistent in the environment and has moderate potential to leach. Phototransformation is not an important process for either of these chemicals. Two major biotransformation products of fluroxypyr-methylheptyl ester and fluroxypyr acid were identified: pyridinol, which is slightly to moderately persistent, and methoxypyridine, which is more persistent. These transformation products have mobility potential in soil but have low to moderate potential to leach to groundwater. In aquatic systems, fluroxypyr-methylheptyl ester partitions into the sediment phase after a few hours, then quickly hydrolyzes to its acid equivalent, fluroxypyr acid. Once fluroxypyr acid is released into the water phase it is expected to slowly transform under aerobic conditions. Fluroxypyr-methylheptyl ester or fluroxypyr acid will not bioconcentrate in fish.

Fluroxypyr is applied by broadcast sprayer. There is a potential that non-target terrestrial and aquatic habitats may be exposed to the chemical as a result of spray drift or runoff. Fluroxypyr-methylheptyl ester does not present a risk to earthworms, birds, small mammals, bees and beneficial arthropods. However, it poses a risk to non-target terrestrial plants and freshwater organisms including aquatic invertebrates, fish, amphibians and algae. Precautionary statements are included on the end-use product Starane II Herbicide label, and buffer zones of five metres (terrestrial habitats) and one metre (aquatic habitat) are required to mitigate risk to non-target plants and aquatic organisms from spray drift. Fluroxypyr acid does not pose a risk to terrestrial or aquatic non-target organisms.

Value Considerations

What Is the Value of Starane II Herbicide?

Starane II Herbicide is a post-emergent herbicide to control specific broadleaf weeds in small grain cereals, rangeland, permanent pasture, industrial and non-cropland areas.

Fluroxypyr formulated as Starane Herbicide (Registration Number 24815), was first registered in Canada in 1997 for control or suppression of cleavers, kochia (including Group 2 resistant biotype), round-leaved mallow, volunteer flax, chickweed, hempnettle, wild buckwheat, and stork's-bill in spring wheat, durum wheat, and spring barley.

Starane II Herbicide, with a higher product guarantee, was registered based on the registration of Starane Herbicide. Starane II Herbicide can be applied as a broadcast treatment at a rate of 0.21-0.41 L/ha in spring wheat, durum wheat, spring barley and oats. Starane II Herbicide may also be applied alone at a rate of 0.42 or 0.84 L/ha for suppression or control of kochia (including Group 2 resistant biotype), respectively, or in a tank mixture with Milestone Herbicide (Registration Number 28517; 240 g/L aminopyralid) at a rate of 0.25-0.5 L/ha for control of broad weed spectrum in industrial and other non-cropland areas.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the label of Starane II Herbicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

To minimize direct contact with fluroxypyr residues on the skin, anyone mixing, loading and applying Starane II Herbicide must wear coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.

Workers must not enter treated industrial and non-cropland areas until residues have dried.

Environment

To mitigate risk to non-target terrestrial plants and aquatic organisms, buffer zones of five metres (terrestrial habitats) and one metre (aquatic habitats) are required during application.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2012-18, *Fluroxypyr)* are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[5] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision, www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/publi-regist/index-eng.php#rrd) or contact the PMRA's Pest Management Information Service.

[5] As per subsection 35(1) of the *Pest Control Products Act.*

Appendix I Comments and Responses

1. **Comments on the interpretation of the rabbit developmental toxicity study and the endpoints selected were received.**

   Response

   The comments made on the Proposed Regulatory Document, PRD2012-18, *Fluroxypyr*, appear to emerge from a comparison between the USEPA and the PMRA endpoints. Although the review of this technical grade active ingredient was a joint effort including the regulatory authorities of the United States of America, Australia, New Zealand and Canada, each regulatory agency performed an independent risk assessment. All of the comments received for toxicology refer to one developmental toxicity study in rabbits (reference number PMRA 2065157). After reviewing the study, the PMRA has set the LOAEL for developmental toxicity at the mid-dose (500 mg/kg bw/day) based on an increased incidence of a developmental variation (retrocaval ureter), while the USEPA has set their developmental LOAEL at the high dose (1000 mg/kg bw/day), also based on an increased incidence of retrocaval ureter. Although the incidence was statistically significant at the high dose only, the PMRA judged the incidence of retrocaval ureter at the mid-dose to be of biological significance and considered it to be the LOAEL (Retrocaval ureter incidences at doses of 0, 100, 500, 1000 mg/kg bw/day; # foetal/litter: 3/2, 6/2, **12/7**, **11/7**; historical control incidence ranges # foetal/litter: 0-10/0-6).

2. **A comment was received which suggested that as a risk reduction measure, mixer/loaders and applicators must follow good agriculture practices.**

   Response

   Risk reduction measures for worker exposure include personal protective equipment, engineering controls, and restricted entry intervals which mitigate potential exposure. However, following good agriculture practices is expected for anyone mixing, loading and applying Starane II Herbicide, since all commercial pesticide applicators must be trained, and licensed or certified by the provincial or territorial pesticide regulatory agency. As such, it does not fall under the scope of risk reduction measures.

3. **A commenter noted that the endpoint EC_{50} = 0.037 mg/L (*Table 10*) should be considered unreliable because the acetone control used in the freshwater *Navicula pelliculosa* study (PMRA 2065294) was found to be contaminated by the test substance. The commenter referred to a newer *Navicula* study in which the lowest endpoint is the 72-h E_bC_{50} of 0.210 mg/L and should be regarded as more reliable for risk assessment purposes.**

   Response

   In the first *Navicula* study, there were two different types of controls included in the study, the algal assay medium with and without acetone. The control without acetone (negative control) was not contaminated by the test substance and could, therefore, be used. The

detected levels of fluroxypyr in the acetone control were within the range of those in the lowest test concentration, and no effects were observed in either of those treatment groups. Also, it should be noted that the endpoints were based on mean measured concentrations and control data were not included in the curve fit. Thus, the contaminated acetone control did not impact the EC_{50} value used in the risk assessment. For these reasons, this study was not rejected and the results were used.

The newer *Navicula* study (summarized in PMRA 2100405) was not considered in the environmental review for the following reasons:

- The study was not an exact duplicate of the first study (PMRA 2065294).
- The concentrations used were above the solubility limit of 0.109 mg/L for fluroxypyr 1-methylheptyl ester.
- The study was not performed in compliance with some criteria of OECD 201 Guidelines: the minimum multiplication factor of 16 was not reached for medium control within 72 hours and the mean coefficients of variation for section-by-section specific growth rates in controls were above 35%.

4. Comments were received, with respect to typographical and/or transcription errors, for some of the end-points reported in the environmental summary Tables 11 and 12 of the Proposed Regulatory Document, PRD2012-18, *Fluroxypyr*.

Response

Some changes have been identified in Table 11 and 12 of PRD2012-18, *Fluroxypyr*, and are listed below:

Table 11:

- The endpoint for *Lemna* exposed to Fluroxypyr methoxypyridine is 14-d EC_{50} = 10.6 mg/L rather than 1.19 mg/L.
- The endpoint for *Anabaena* exposed to Fluroxypyr methoxypyridine is 96-h EC_{50}=1.19 mg/L rather than 3.37 mg/L.

Table 12:

- For acute daphnia, the resulting RQ should be <0.00070 (Fluroxypyr acid) and <0.0011 (Pyridinol), rather than <0.0006 and <0.0005, respectively.
- For acute rainbow trout the resulting RQ should be 0.0069 (Pyridinol) rather than 0.014.
- For freshwater algae, EC_{50} is 1.19 mg/L (Methoxypyridine) and RQ is <0.049 (Methoxypyridine) rather than 3.37 mg/L and 0.0172, respectively.
- For vascular plant, RQ is <0.0433 (Fluroxypyr-MHE), EC_{50} is 10.6 mg/L (Methoxypyridine) and RQ is 0.0055 (Methoxypyridine) rather than <0.00432, 1.19 mg/L and 0.0048, respectively.

Overall, these changes have no impact on the results of the risk assessment.

References

PMRA Document Number	Reference
2100405	2009, Assessment Report – Public Version – Initial Risk Assessment Provided by the Rapporteur Member State Ireland for the Existing Active Substance Fluroxypyr Upon Submission in the Framework of the Renewal of the Inclusion of a First Group of Active Substance in Annex I to Council Directive 91/414/EEC in Accordance With Commission Regulation (EC) No 737/2007. DACO: 12.7